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Original Research Article

To compare the efficacy of two probiotics in acute non bloody diarrhea

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ABSTRACT

Background: According to WHO watery diarrhea is defined as passage of 3 or more loose stools without blood during preceding 24 hrs. End point of diarrhea was defined as passage of 3 stools of formed consistency. The objective of this study was to compare the efficacy of two groups of commercially available probiotics in treating children hospitalized with acute non-bloody diarrhea on the basis of duration of stay in hospital, frequency of stool per day and duration of requirement for intravenous fluid. And to compare the results of probiotics in Rotavirus antigen positive children.
Methods: A prospective interventional study was conducted in Holy Family Hospital, New Delhi in children aged between 6 months - 5 years hospitalized with acute non bloody diarrhea with 30 children in each group.
Results: Total 123 children (6 months - 5 years) admitted in hospital with acute diarrhea, out of which 6 turned out to be bloody, 5 could not be followed up and 3 went LAMA. Finally 109 children with 68 males (62%) with male:female ratio of 1.65. Total 109 children (68 males) were included - Group A (33), 48 in Group B (48) and 28 in Group C (28). In a lateral study, Group A (11), Group B (23) and Group C (10) were Rotavirus positive. 49 children (45%) admitted with stool frequency of 5-10 times per day. Majority of children presented with symptoms like vomiting (68%), fever (55%), decrease oral intake (45%), decrease urine output (25%). Majority of patients 92 children (84%) were between 6 months to 2 years. 44 children (40%) were Rotavirus antigen positive.
Conclusions: There is no statistical significant advantage of adding probiotics for treating acute non bloody diarrhea including Rotaviral.

Keywords: Diarrhea, Rotavirus

INTRODUCTION

According to WHO watery diarrhea is defined as passage of 3 or more loose stools without blood during preceding 24 hrs. End point of diarrhea was defined as passage of 3 stools of formed consistency.[1] Diarrheal disorder in childhood accounts for a large proportion (18%) of childhood death with an estimated 1.8 million death per year globally. The WHO suspects there are more than 700 million episodes of diarrhea annually in children less than 5 year of age in developing countries while global mortality may be declining. According to WHO, diarrhea itself causes >20% mortality under 5 years of age in India. The overall incidence of diarrhea remains unchanged at about 3.2 episodes per child per year.[1] Gastroenteritis is due to infection acquired through the feco-oral route or by ingestion of contaminated food or water. Gastroenteritis is associated with poverty, poor environmental hygiene and developmental indices. Enteropathogens that are infectious in small inoculums

(*Shigella, E. coli, Norovirus, Rotavirus, Giardia, Cryptosporidium parvum, Entameba histolytica*) can be transmitted by person to person contact whereas others such as cholera are generally a consequence of contamination of food or water supply.[2,3] Across the globe around 12 million children die each year before they reach their 5th birthday. Acute diarrheal disease ranked 2nd amongst all infectious diseases as killer in this age group. India alone loses 0.6 million children each year due to this scourge. Management of acute non bloody diarrhea includes fluids & supportive care in form of Zinc.[2,4] The management in the form of giving probiotics has long been advocated. Probiotics are by definition of WHO and FAO of United Nations are living microorganism which when administered in adequate amount confer a health benefit to the host.[3] Rotavirus and other gastroenteritis viruses not only are major causes of pediatric mortality but also lead to severe morbidity.

METHODS

A prospective interventional study was conducted in Department of Pediatrics in Holy Family Hospital, New Delhi during the period January 2012 to July 2012.

Inclusion criteria

All admitted children between 6 months to 5 years of acute non bloody diarrhea of less than 72 hrs.

Exclusion criteria

Diarrhea more than 72 hours with severe dehydration (WHO classification). Severe malnutrition, other systemic illness like encephalopathy, meningitis, dyselectrolemia, on probiotics before admission.

Methodology procedure

History, physical examination, stool examination, Rotavirus antigen test (rotaviral antigen quick test by generic assays Gmbt kit), duration of intravenous fluids, duration of hospitalization and total period of illness were recorded. They were divided into Group A: no probiotics, Group B: Probiotic (Bacillus clausii, 2 billion/day), Group C: Probiotic (Lactobacillus acidophilus, L. ramnosus, Bifidobacterium longum and Sacchromycis bollard 2.5 billion/day). All patients were treated with zinc, ORS and intravenous fluids (if needed) and followed till 2 diarrhea free days.

Well written consent was taken with parents and hospital ethical committee clearance was taken.

Statistical analysis

Statistical analysis was performed by the SPSS program for Windows, version 17.0 .Continuous variables are presented as mean ± SD and p value.

RESULTS

Total 109 children (68 males) were included - Group A (33), 48 in Group B (48) and 28 in Group C (28). In a lateral study, Group A (11), Group B (23) and Group C (10) were Rotavirus positive.

Table 1: For total 109 children's - all results in days (Mean±SD).

	Group A	Group B	Group C	P value
Duration of IV fluids	1.71±0.72	1.79±0.85	1.56±0.75	0.464
Duration of hospital stay	2.88±0.85	3.19±0.89	2.79±0.87	0.111
Duration of illness	5.03±1.26	5.48±1.41	5.46±1.37	0.298

Table 2: For Rotaviral diarrhea.

	Group A	Group B	Group C	P value
Duration of IV fluids	1.55±0.52	1.91±0.95	2.0±0.82	0.334
Duration of hospital stay	2.73±0.47	3.17±1.03	3.20±0.79	0.392
Duration of illness	4.82±0.75	5.65±1.37	6.40±1.17	0.016

DISCUSSION

Diarrhea is caused by number of bacterial, viral and parasitic pathogens.[1] In Europe, North America and other industrialized countries the vast majority of episodes of diarrhea are caused by a viral pathogens that exhibit distinct winter seasonality. In developing countries with poor hygiene and sanitation, enteric bacteria and parasites are more prevalent and typically peak during summer months. Children in developing countries are exposed to wide range of causative organism at a very early stage and suffer numerous episodes of diarrheal illness as a result. The effect of probiotics in management of acute diarrhea have been postulated and understood to be

because of mechanism like immonological tolerance, producing bacterocins to act as local antibiotics, inhibiting pathogen growth by luminal pH, improving mucosal integrity by stimulating mucin production and by decreasing potent proinflammatory cytokines and enhancing the production of antiinflammatory cytokines.[2-4] In a published summary of 73 studies of children who sought care for diarrhea in 33 countries Rotavirus was the most frequently identified.[5,6] Optimal management of diarrhea patients including choice of therapy differs in invasive and noninvasive diarrhea. Role of probiotics in management of diarrhea have long been advocated.[5,6] Probiotics are live microorganism (in most cases bacteria) that are similar to beneficial microorganism found in human gut. They are also called "friendly bacteria" or "good bacteria".[6,7] Probiotics are available to consumers mainly in the form of dietary supplements and food. They can be used as complementary and alternative medicine. One widely used definition by World Health Organisation and Food and Agriculture organisation of UNITED NATIONS is the probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit on the host".[8] Probiotics have been selected from members of normal healthy intestinal microbiota, most of them belonging to Lactobacillus or Bifid bacterium, but new probiotic microbes from other species being introduced regularly.[9]

Male predominance (60%) has been noted in our study as well by Chen et al and Heuilan et al in their respective study majority of the patients (84%) were between 6 months to 2 years, similar results were found in study from Ghana by Reither et al, where majority of patients were under 5 years.[10-12] In our study almost 50% of children were between 6 months to 11 months , 52.3% of them (34 in number) were non Rotavirus and 47.7% (21 in number) were Rotavirus positive. It was consistent with study by Meritol Stanly from Chennai where 60% of children with diarrhea were of age group between 6 months to 11 months. We had almost 33% children between age group 12 months to 24 months and 15 % above 24 months, similar with study by Meritol Stanly (40%) between 12 months to 24 months and lowest in more than 2 years.[13]

About 73% children in our study presented with symptoms less than 48 hours, this is consistent from study from Ghana by Reither et al, in which mean duration of diarrhea at presentation was 72 hours.[12] After loose stools, the most common presenting feature in our study subjects were vomiting (68%), markedly higher than study of Reither et al (14%), while study by Ozlem Erdogam from Turkey showed vomiting in almost 49.3% children at presentation.[14] Fever was next common presenting complains (55%), which is less than Reither et al study 83%.[10]

In this study 44 children (40%) children were Rotavirus positive, which is higher than study done by Samantray et al (33.3%) in Delhi.[15] Other centres in India have reported wide range of incidence, like Steinhoff MC et al-22% in Vellore, 66% by Maya PP in Calicut, 25% by Anand et al in Tirupati and 37.9% by Vidya Nerurkar in Mumbai.[16-19] As per presenting symptoms of Rotavirus diarrhea along with loose stools 33 children (75%) presented with vomiting, higher than study done by Ozlem Erdogem from Turkey (49.3%).[14] 23 children (52.3%) presented with fever, 21 (47.7%) with decrease oral intake, 12 (27.3%) with decrease urine output along with loose stools. (Such observations for other symptoms were not looked in other study related to rotavirus diarrhea).

In this study there was decrease in number of patients with loose stools from day 3 to day 4 (P- value> 0.05) in all the three groups (for 109 children), from 76% to 27% in group A, from 85% to 37% in group B and 85% to 53% in group C [P - value 0.140(>0.05)]. (Such observation with absolute number of patients was not done in other relevant studies). As per frequency of loose stools, there was reduction from day 2 to day 3 [Median of 1-6, 1-16 and 2-14 in respective groups, (A,B and C) for total 109 children on day 3, (p-value:0.197;>0.05)] In a meta-analysis done by Cornelius Von et al there was reduction of diarrheal frequency of 1.6 stools/day on day 2 (95% CI - 0.7 - 2.6 fewer stools/day) in patients on lactobacillus therapy.[20] In a study by Raza et al there was reduction in frequency of vomiting and loose stools on day 2 with lactobacillus therapy.[21] While in a study by Sarker et al using L papacasei strain ST in 230 male infants and young children aged 4 to 24 months in Bangladesh, found reduction in stool output (225±218 ml/kg versus 381±240 ml/kg) and stool frequency (27.9±17 versus 42.5±26) in treatment group on day 2.[11,22] There was a study from Pakistan by Billo and colleagues in 100 children aged 2 months to 12 months using Saccharomyces boulardii for 5 days and they found reuction in diarrhea episodes to from 4.2/day in placebo group to 2.7/ day in the probiotic group (on day 3 of treatment).[23]

As per duration of intravenous fluids in days in our study, there was drop in requirement of intravenous fluids from day 2 to day 3 in all the three groups of study. It decreased from 36% to 12 % in Group A, from 31 % to almost 21% in Group B and 35% to almost 4% in Group C [P- value 0.067 (>0.05)]. Only 2% and 3% patient needed iv fluids till day 4 in group B and in group C respectively. (Such observation was not made in earlier studies related to diarrhea).

As per duration of stay in hospital in days the mean duration of stay in Group A was 2.88±0.85, 3.19±0.89 in Group B and 2.79±0.87 days in Group C (p-value 0.111: >0.05), while study by Krugol and Koturoglu from Turkey published a study with RCT (n = 200) showing that Saccharomyces boulardii for 5 days reduced the length of the hospital stay from 3.9 days to 2.9 days (P-value< 0.05).[24]

Total duration of illness in days in our study was 5.03±1.26 in Group A, 5.48±1.41 in Group B and in Group C 5.46±1.37 [p-value 0.298 (>0.05)]. In other studies there was significant reduction of duration of diarrheal illness in intervention group receiving lactobacillus GG, like reduction of diarrheal illness from 6 days to 3 day by Guarino et al, from 71.9±35.8 hours to 58.3±27.6 hours (p- value 0.03) by Guandalini et al.[25,26] In a study by Majamaah et al mean duration was 1.8 days (reduced by 0.8 days) who received L. GG, 2.8 days (reduced by 1.2 days) who received L. rhamnosous and 2.6 days (reduced by 1.4 days) who received Streptococcus thermophilus and L. delbruchis.[27] Szajewska et al examined studies using Saccharomyces boulardii in a meta - analysis involving four RCTs (n = 619) in children, found reduction in duration of diarrhea (-1.1 days; 95% CI: -1.3 to -0.8).[28]

In 2005 Allen and colleagues examined 23 studies of probiotics use for acute diarrhea in adults and children, in a subset of 12 studies performed in infants and children, mean duration of diarrhea was reduced by 29.2 hours in subjects taking probiotics (95% CI: 25.1- 33.2;P <0.00001).[29] While study by Szymanski et al who randomised 87 infants and children aged 2 months to 6 years to L rhamnosus strain 573L/1, found a non-significant trend in non-rotavirus infection group (84 hours of diarrhea in the treatment group versus 96 hours in placebo group) and a Peruvian RCT by Salazar - Lindo et al in 179 infants and children aged 3 months to 36 months did not find benefits of L rhamnosus using an enriched milk formula compared with placebo.[28,30]

Cochrane review on probiotics published in 2010 involving 63 trials which included 8014 children was of view that probiotics reduces the duration of diarrhea by almost 25 hours (24.76 hours; 95% CI-15.9 -33.6 hours; n = 4555, trials = 35), reduces risk of diarrhea lasting 4 or more days by 59% (Risk ratio - 0.41; 0.32 to 0.53: n = 2853 , trials = 29) and results in fewer loose stools on day 2 (mean difference 0.80; 0.45 to 1.74; n = 275, trials = 20). To compare the similar outcomes in Rotavirus diarrhea we found the results were consistent to findings as a whole group. As per frequency of stools the median was 4 in Group A, 5 in Group B and 9 in Group C (p-value 0.028:<0.05), probably because of small number of patients in Group A. (Such observation was not made in other studies related to Rotavirus diarrhea and probiotics).

For duration of intravenous fluids in Rotavirus diarrhea, it was mean of 1.55±0.52 in Group A, 1.91±0.95 in Group B and 2.0±0.82 days in Group C [P_value 0.334, >0.05]. (Such observation was not made in earlier study related to probiotics and rotavirus diarrhea). For stay in hospital for Rotavirus diarrhea the mean duration the mean duration of loose stools in Group A was 2.73± 0.47, in Group B 3.17±1.03 and in Group C 3.20±0.79 (P_value 0.392:>0.05).

As per total period of illness in Rotavirus diarrhea was 4. 82±0.75 in Group A, 5.65±1.37 in Group B and 6.40±1.17 in Group C (P-value 0.016:<0.05) in mean days (it could be because of small number of patients), while study from Guarino et al it was reduced from 6 days to 3 days in group of patients on Lactobacillus GG.[25] It was reduced from 76.6±41.6 hours to 56.2±16.9 hours (p-value <0.0008) in study by Guandalini et al when patients received lactobacillus.[26] In a study by Szymanski et al there was significant reduction in duration of illness in Rotavirus diarrhea (76 hours versus 115 hours in the placebo group).[28]

In a study by Ozlem Erdogem from Turkey there was significant reduction of mean duration of illness as 4.1±1.3 days (P - value <0.001) in children on Bifidobacterium lactis.[14] In the same study they showed reduction in symptoms like vomiting and fever in follow up in interventional group (such observation on daily basis was not looked in our study although there were symptomatic improvements in fever and vomiting in all the three groups).

In a study by Grandy G et al median duration of diarrhea was 58 hours who were on probiotics which was shorter than control group (84.5 hours) (P- value 0.04: <0.05) but no effect on duration of hospitalisation (p- value 0.31) in Rotavirus diarrhea.[31]

Today we have large number of clinical trials on the role of probiotics in treating children with acute watery diarrhea. They consistently show a statically significant benefit and moderate clinical benefit of few probiotics strain mostly Lactobacillus GG and Saccharomyces boulardii in acute watery diarrhea primarily rotavirus in infant and young children of developed counteries by reduction of rotaviral illness by little over one day.[32] The research is emerging for clinical benefits of multiple strains of probiotics although there is no genuine rationale for combining them. The present study disproves the use of probiotics in terms of said clinical benefits as well as no significant advantage of multiple strain probiotics over single strain even in cases of Rotaviral diarrhea.

CONCLUSION

Diarrhea remains one of the most common causes for hospital admission in children less than 5 years of age. Children have high risk of repeated diarrheal illness. The incidence of Rotavirus diarrhea is high in patients requiring hospital admission. The probiotics as per treatment protocol for acute watery diarrhea has questionable efficacy at least in this population. There is no advantage of adding probiotics (single strain or multiple strains used in our study) in management of acute watery diarrhea at least in terms of improvement in frequency of stools, reduction in duration of intravenous fluids, duration of hospital stay or in total period of illness. Role of probiotics (single strain or multiple strain

used in our study) for Rotavirus diarrhea also does not appear to have encouraging results. There is need of larger studies in Indian population before accepting probiotics for management of acute non bloody diarrhea.

There is no statistical significant advantage of adding probiotics for treating acute non bloody diarrhea including Rotaviral.

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